MEDICAL STAFF CONFERENCE

Diseases from Vietnam

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* The Medical Grand Rounds this morning is being devoted to the medical fallout of our brisk foreign policy. The presentation of patients as well as the discussion will be given by Lieutenant Colonel John J. Deller. Dr. Deller we know as an old friend, since in addition to his army training he spent one year as a Fellow in Endocrinology and Metabolic Diseases here at the University of California. We are delighted to welcome him back and have him introduce both his topic and his patients.

DR. DELLER:† Thank you, Dr. Smith.

This morning I would like to review some of the medical problems seen in this country but which have originated in Southeast Asia. These problems have significance for physicians here in San Francisco; they are not remote tropical diseases found only in a textbook. Currently there are over 500,000 Americans in Vietnam. With the present rotation policy, these 500,000 Americans will return to the United States within a year, and with them will come tropical diseases.

Basically the medical community is faced with two problems: the recognition of diseases imported into this country for the sake of the "host patient" himself and, less immediate but more far-reaching, a significant public health problem in the introduction of new diseases into this country. I will deal mainly with the first of these considerations and only touch upon the potential of the latter.

It takes less than 20 hours to fly from Saigon to San Francisco. This brings the fighting-front fairly close. Thus, it is not at all unreasonable for us to expect any disease seen at a battalion clearing company or an evacuation hospital in Southeast Asia to appear at a community hospital in this country. Realization of this fact emphasizes the importance of tropical medicine in the United States, not only now but in the future. With increasing air traffic around the world, tropical diseases will be seen more and more in this country. Only by having a keen awareness of these diseases will we be able to make prompt, accurate diagnoses. Because some of these diseases are potentially fatal, early recognition may be critical.

In the limited time available, I shall concentrate on a small group of febrile illnesses which, because of their long incubation period, are likely to be seen in this country. Many of these patients will be seen by private physicians because most of the returning soldiers are either discharged from the service within a few days of arrival in the States or are given a 30-day leave.

It was from necessity that we became interested in tropical febrile diseases at the 93rd Evacuation Hospital in Vietnam. At first we had only the usual textbook knowledge of these diseases. It was very frustrating to admit large numbers of patients having a variety of indistinguishable febrile illnesses. We studied a number of these cases to establish some diagnostic criteria. When you read the chapters on tropical medicine in the standard textbooks of medicine, you find that all of the tropical febrile diseases seem to melt together and that there appear to be very few distinguishing features. In order to organize an approach to these illnesses, I have grouped them into five major disease categories (Table 1). The major arborvirus diseases seen in Southeast Asia are two in number: dengue, with which you are probably familiar, and chikungunya, which is esoteric by American standards. These in addition to scrub typhus, leptospirosis, and malaria constitute the biggest medical problems. Melioidosis is of significance because of its

*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†LTC John J. Deller, Jr., Deputy Chief, Department of Medicine, and Chief, General Medical Service, Letterman General Hospital, San Francisco.

seriousness. (This list omits venereal disease, by far the commonest infectious disease among troops in Southeast Asia.)

Table 2 is taken from our original study in which we attempted to define the various clinical manifestations of these febrile tropical illnesses. The diagnoses were proven by virological, bacteriological, or serologic tests.[1]

Dengue

Dengue is the most common arthropod-borne virus disease affecting our troops in Southeast Asia. A widely known disease, dengue was first recognized in the 1780s in Philadelphia—certainly no tropical climate. Since that epidemic the disease has cropped up from time to time throughout the country, mostly in army camps. The mosquitoes necessary for transmission of this disease do exist in the United States.

In Vietnam we were confronted with the problem of differentiating dengue from a number of more serious diseases. As will become apparent, fever, chills, and headache are characteristic of most of the tropical febrile diseases. However, it is important to know how high the fever goes and where the man was when he became ill, because, knowing these two simple facts, one can often distinguish between arborvirus diseases on the one hand and the "jungle-borne" diseases on the other. For example, patients with arborvirus infections rarely have temperatures above 104° F. This is an extremely important differential point because almost invariably a patient with malaria will have a fever rise above 104° F within the first 48 hours.

The arborvirus diseases, dengue and chikungunya, are transmitted primarily by the Aedes mosquito, an urban dweller. As a consequence, these diseases are not likely to be encountered in the jungle but are most frequently seen in an urban area or base encampment. Thus by asking the patient where he was within the 2 or 3 weeks preceding onset of symptoms, one can often predict whether the patient has an arborvirus disease or a "jungle-borne" disease such as malaria, leptospirosis or scrub typhus.

The symptoms of dengue are not distinctive. Three-quarters of the patients have a "flu-like" illness with malaise, backache, anorexia, fever, and often severe frontal headache. They may present with lymph adenopathy, an important physical finding because patients with malaria do not have adenopathy and in patients with scrub typhus adenopathy develops only after several days of illness. A fleeting macular rash is present in at least one-third of the patients, and spontaneous petechiae occurring within this setting, especially on the lower extremities, are almost diagnostic for the arborvirus diseases. The tourniquet test may be positive in patients with dengue without an associated reduction in platelet count.

The course of dengue is variable. Generally fever and symptoms subside within 5 to 7 days, and few patients have a prolonged convalescence.

TABLE 1.—*Major Febrile Tropical Illnesses in Southeast Asia*

Arborvirus Diseases
Dengue
Chikungunya
Scrub Typhus
Leptospirosis
Malaria
Melioidosis

TABLE 2.—*Differential Features of Patients Having Dengue, Chikungunya, Scrub Typhus, Leptospirosis, and Malaria*

	Dengue	*Chikungunya*	*Scrub Typhus*	*Leptospirosis*	*Malaria*
Epidemiology					
Camp, urban	†††	†††	—	—	—
Jungle	—	—	†††	†††	†††
Fever, F					
<104	†††	†††	†	†††	—
>104	—	—	††	—	†††
Arthralgias	—	†††	—	—	—
Tender adenopathy	†† (Early)	†††	††† (Later)	†	—
Tender liver or spleen	—	—	††	††	†††
Rash	†	††	††	—	—
Petechiae or positive tourniquet test	†	—	—	—	—
Leukocyte count per cu mm					
<5,000	††	††	—	—	—
>5,000	†	†	†††	†††	†††
SGOT >50 units	—	—	—	—	††

SGOT = serum glutamic-oxaloacetic transaminase; — = less than 25 percent; † = 25 to 49 percent; †† = 50 to 74 percent; ††† = 75 to 100 percent.

Adapted from Annals Inter. Med., 66:1129, 1967 and USARV Med. Bull., 2:23, 1967.

Chikungunya

The second arborvirus disease which may be acquired in Vietnam and transported back to this country is chikungunya. This disease was first recognized in Tanganyika in 1952 when an epidemic characterized by high fever and severe polyarthritis occurred among the natives. It was, however, self-limited. Fortunately, Dr. Ross[2] collected blood from many of the affected patients along with pools of Aedes mosquitoes, and in 1956 he isolated a new virus to which the name chikungunya was given—the natives' description, which means "that which bends up the joints."

Since the recognition of that original epidemic, chikungunya has been identified throughout Southeast Asia, southern parts of Africa, and India. It has had a wide spectrum of clinical features ranging from severe polyarthritis, which so far as I know has been self-limiting, to a dengue-like illness with mild arthritis, to hemorrhagic fever. The same virus has been cultured from all of these clinical varieties.

The one feature that distinguishes this disease from dengue is the arthritis. Even though dengue has been referred to as "break-bone fever," it is not associated with true arthritis. Severe myalgias and perhaps arthralgias may occur with dengue, but not arthritis. The polyarthritis of chikungunya is of great interest, for it represents an example of a known viral disease, from which an organism can be readily cultured, that can mimic both rheumatoid arthritis and acute rheumatic fever. It is very much like the epidemic polyarthralgia, which again mimics rheumatoid arthritis, reported in Australia and New Guinea. Chikungunya so closely resembles rheumatoid arthritis that our first three patients presenting with fusiform swelling of the proximal interphalangeal joints and bilateral synovitis of the wrists were initially diagnosed as having acute arthritis.[3] However, patients with chikungunya improve spontaneously and, although the arthritis may linger for several weeks, it does not develop into chronic arthritis. However, it is conceivable that if a viral disease similar to chikungunya had a strong antigenic potential, it could initiate an auto-immune reaction and lead to a chronic form of arthritis.

Except for the arthritis, chikungunya in American troops has been a mild dengue-like illness. It has not produced the severe crippling arthritis of the type reported in Tanganyika, nor has it caused hemorrhagic fever as occurs in dengue. It is a disease that should be considered in a Vietnam veteran who has an acute febrile illness.

It is important to recognize these two arborvirus diseases in order to distinguish them from diseases that are more important from the standpoint of morbidity and mortality.

Scrub Typhus

Scrub typhus is caused by a mite-borne rickettsia and presents with a typical triad of rash, eschar, and a positive therapeutic response to tetracycline. With these prominent features, it is usually easy to diagnose; unfortunately, not all cases behave this simply. Sometimes the eschars are hidden and may be overlooked on physical examination.

Like malaria, scrub typhus occurs in the jungle. The mites that carry the rickettsial organism breed in heavily forested areas of Vietnam; hence a history of a jungle environment is important. It has been said that these mites live and breed on the larvae of the Anopheles mosquito. I am not sure that this theory holds up, but at least the two diseases commonly occur together; indeed, malaria and scrub typhus may occur simultaneously in the same patient. The fever, chills, headache, malaise, adenopathy and backache common to all of these tropical diseases are also characteristic of scrub typhus. In addition, severe conjunctival injection, which we usually associate with leptospirosis, is common in scrub typhus. The most important features are a macular rash, which is usually not as fleeting as the rashes of the arborvirus diseases, and an eschar. The eschar typically resembles a cigarette burn. It is not surrounded by significant inflammatory reaction and usually has a black necrotic center with a narrow rim of erythema. There is no associated lymph angitis or lymph adenitis. This lesion is important to recognize because in melioidosis, which I will discuss later, a skin inoculum can present in a similar manner, except that there is a much greater reaction and associated lymph angitis.

It is important to treat suspected scrub typhus with tetracycline. Of the tropical diseases, only scrub typhus responds dramatically to tetracycline therapy (1 gram every hour for four doses followed by 1 gram every 6 hours for 7 days). Within 48 hours, and often within 12 hours, there is a dramatic drop in fever. It is important to treat scrub typhus early, for if the disease goes untreated for 2 weeks, there is an alarming morbidity. Most of our patients in whom the disease was not recog-

nized for 2 weeks had to be evacuated to the United States and were ill for 6 to 8 weeks.

Leptospirosis

In leptospirosis the patient is not bitten, but has only to come in contact with leptospires breeding in the mud banks and rice paddies. Leptospirosis closely mimics dengue and scrub typhus and has very few distinguishing characteristics. It has been called "pseudodengue." It most closely mimics scrub typhus because of the generally high, spiking fevers. Conjunctival suffusion is an important sign, but it does not distinguish leptospirosis from scrub typhus. Gastrointestinal complaints and hepatic tenderness are common, which makes for confusion of this disease with malaria. A laboratory finding of leukocytosis is occasionally helpful, since most of the other tropical diseases are characterized by a normal leukocyte count or by leukopenia.

Leptospirosis actually encompasses an entire spectrum of diseases from a benign, self-limited form such as our troops are experiencing to a severe, hemorrhagic disease with severe jaundice and renal failure. Since our troops fortunately have acquired the benign form, there have been no serious complications. The benign form of leptospirosis is self-limited and requires no specific therapy.

Malaria

Malaria is the tropical disease which is of most concern to military physicians because it accounts for the largest number of patients. The malaria seen in Vietnam may be quite different from that seen in San Francisco. About 98 percent of the cases of malaria diagnosed in Vietnam result from *Plasmodium falciparum,* whereas 80 percent of the cases seen in this country result from *Plasmodium vivax.* The reason for this difference is the chloroquine-primaquine chemoprophylaxis or "suppressive therapy" program that is being used in Vietnam. Usually once a soldier leaves the endemic area, he neglects to take the drugs, even though he is given an 8-week supply, and with discontinuance of therapy the disease becomes manifest. Of 29 consecutive patients with vivax malaria admitted to Letterman General Hospital within the past year, not one had taken the medication after getting off the airplane! Subsequently a larger group of patients who did not have malaria after returning to this country were surveyed, and 60 percent of them had not taken the chemoprophylaxis after leaving Vietnam.[4]

The reason so much falciparum malaria is seen in Vietnam is that the current drug therapy is not suppressive for *Plasmodium falciparum.* In the last year there have been more than 2,000 cases of malaria diagnosed in American soldiers in this country. This figure could probably be expanded many times by including in it those patients who have left the service and therefore are not reported to the Surgeon General.

Malaria is generally easy to diagnose. All one needs is a high index of suspicion, a blood smear, and a technician or physician who knows how to interpret the smear. The majority of patients with malaria will have fever above 104° F within the first 72 hours of illness; frequently the temperature goes to 105° or 106° F. The differentiating feature is that such elevations are extremely rare with the other tropical diseases. Of course the shaking chill, a hallmark of malaria, is generally present, accompanied by headache and a variety of gastrointestinal complaints in over three-quarters of the patients. The most remarkable feature about the physical examination is the absence of specific findings. Except for percussion tenderness over the liver or spleen, or both, the examination is usually negative unless the patient has one of the major complications. Notably absent are the "typical" fever patterns and splenomegaly found in textbook descriptions of malaria. This absence is attributable mainly to prompt diagnosis and early treatment.

For the diagnosis of malaria, a high index of suspicion is critical. Once malaria is considered, a series of blood smears, both thick and thin, should be done to confirm the diagnosis. If you're lucky, on a thin smear you will see typical ring forms. Frequently, however, the thin smear will not reveal ring forms within the erythrocyte, and a thick smear will be necessary. The parasites may be fragmented and difficult to diagnose. In falciparum malaria the ring forms are only about one-fifth as large as the vivax forms. The gametocytes of falciparum malaria, however, are quite typical and easily recognized. Unlike the diseases previously discussed, which manifest themselves within 3 weeks, malaria may have a long latent period. Most of the vivax malaria in this country is diagnosed in patients who have left an endemic area more than 50 days before; therefore, this disease is very likely to be seen by private physicians.

The treatment of malaria has undergone several changes since the appearance of resistance strains

of *Plasmodium falciparum* in Vietnam. Currently, however, the proper treatment can effect a cure in probably 98 percent of cases. In my personal experience with more than 1,200 patients at one hospital, 20 of whom had cerebral complications and three of whom had renal failure, there were no fatalities. Standard treatment for vivax malaria has not changed, as *Plasmodium vivax* has not demonstrated any resistance to chloroquine and primaquine. *Plasmodium vivax* continues to go through reproductive cycles within the reticuloendothelial system; therefore, primaquine is given for at least 14 days in an attempt to eradicate the parasites in this "exoerythrocytic phase."

The treatment schedule for *Plasmodium vivax* infection is as follows: chloroquine phosphate, 1.0 gram (600 mg base) immediately, followed by 0.5 gram in 6 hours and 0.5 gram daily for 2 days. Primaquine, 15 mg base, is given daily for 14 days.

Since as high as 50 percent of *Plasmodium falciparum* infections acquired in Vietnam have been relatively resistant to chloroquine, patients with this infection must be treated with quinine. Quinine, when used properly, is a relatively safe drug. When it is used alone, there is perhaps a 5 to 10 percent failure rate; however, the addition of pyrimethamine (Daraprim®) and possibly a sulfone (Dapsone®) or sulfa drug will approach a 100 percent cure rate for initially treated *Plasmodium falciparum*. Currently, triple therapy for falciparum malaria is recommended. The treatment schedule is as follows: quinine, 650 mg every 8 hours for 10 to 14 days, followed by pyrimethamine, 25 mg, every 12 hours for 2 to 3 days and Dapsone®, 25 mg, given daily for 28 days. Many patients who were treated for *Plasmodium falciparum* in the past have had "recurrences" with *Plasmodium vivax* simply because they did not receive any primaquine.

Table 2 reviews the major points in differential diagnosis of the disease most likely to mimic malaria in a person returning from Vietnam. Where the infection was acquired and how high the temperature rose may be the two most important clues as to whether one is dealing with a treatable infection (malaria or scrub typhus) or a self-limited one.

Melioidosis

Melioidosis may be relatively new to most of you. It was originally recognized in Rangoon in 1912 by Whitmore and Krishnashwami, who reported on a number of street beggars dying with what appeared to be distemper because of the tremendous frothy sputum produced before death. A glanders-like microorganism was subsequently isolated and given the name *Malleomyces pseudomallei*. This disease was next recognized about 5 years later in ante mortem studies by Fletcher and Staunton in Malaya in 1917. Melioidosis has subsequently been found in a variety of forms, most simply classified as follows:

- Acute—pneumonic and septicemic
- Chronic—pulmonary and systemic
- Subclinical—serologic evidence only

The acute form can present as overwhelming pneumonia or as septicemic illness which usually terminates as pneumonia. The chronic variety can masquerade as tuberculosis. This is the type with which I think we should concern ourselves because this is the type that may well be seen here in San Francisco. The chronic variety may also present with manifestations such as chronic draining abscesses or osteomyelitis. It has also been shown that there is an "iceberg effect" in this disease, in that there have been a large number of cases with only serologic evidence of past exposure to this infection. In one Thailand study, approximately 8 percent of the population tested had serologic evidence of previous contact with this organism. Although we are not seeing a large number of cases of melioidosis, there have been more than 60 cases reported since May 1966, in Americans in Vietnam or recently returned from there. It is an important disease because it may be lethal in the acute form and also because of the possibility of transplantation into this country. The organism is ubiquitous.

A keen awareness of the clinical spectrum of melioidosis is the key to diagnosis. A chest roentgenogram will often provide the immediate clue. The organism *Pseudomonas pseudomallei* will grow readily on blood agar media; in fact, sometimes it grows so readily that it is thought to be a contaminant. A smear from the culture, stained with either Gram's or Wayson's stain, provides a clear-cut diagnosis in most cases. The organism appears as small pleomorphic, Gram-negative, bipolar rods that resemble small safety pins. Further identification can be made by sugar fermentation studies or specific serologic tests.

I would like to review briefly the major ways in which this disease may present. In our febrile dis-

ease study, we encountered two cases of the septicemic illness which presented with a cutaneous ulcer (presumably the site of entry of the organism), spiking fever, tremendous cellulitis and lymph angitis, and eventually meningitis and pneumonia. The two patients died without diagnosis having been made. Although they were treated with a large number of antibiotics, there was no obvious effect on the illness. This disease in its septicemic form is almost uniformly fatal when unrecognized.

The clinical course of the acute pneumonic variety varies from death within hours to death within days. It is an overwhelming infection; in fact, it is the most rapidly progressive pneumonia that one is likely to encounter. We saw one patient who had acquired this disease, so far as we know, within 5 hours of his death. In this rapidly progressive form, the disease is probably untreatable and is very much like plague pneumonia.

The form of disease which we are now seeing in this country is the chronic, more benign pulmonary infection which often presents with cough, low-grade fever and a roentgenographic appearance which immediately conveys the impression of tuberculosis. A negative tuberculin test and a history of travel to an endemic area should alert one to this disease.

The treatment of *Pseudomonas pseudomallei* infection will vary with the clinical type of disease. When we were first confronted with the acute varieties in Vietnam, we used standard antibiotic schedules, including novobiocin and chloramphenicol. Despite such therapy our first five patients died. We found on serum inhibition studies that even in the undiluted serum there was no inhibition of growth of the *Pseudomonas pseudomallei* with the antibiotic schedules used. We eventually found that a combination of massive doses of chloramphenicol, novobiocin and kanamycin was necessary to arrest the overwhelming infection. Doses as high as 12 grams of chloramphenicol, 3 grams of kanamycin and 6 grams of novobiocin are necessary. With such treatment the next five patients survived. Such heroic therapy, however, has not been necessary with the more chronic variety of disease. It can be treated with as little as 1.0 gram of tetracycline daily. Naturally, sensitivity studies are required in every case.[5]

In summary, it should be emphasized that one must maintain a high index of suspicion of melioidosis in a patient who has been in an endemic area. This disease may lie dormant for years. In the French experience in the 1940s the disease was cropping up in France as late as 3 years after the return of troops from Southeast Asia.

QUESTION: What is the policy concerning blood transfusions from Vietnam returnees?

DR. DELLER: I believe the current policy is that no one who has been in an area endemic for malaria should be a blood donor for a minimum of 2 years, and this may be revised to exclude such potential donors indefinitely.

DR. SCHMID:* In cases of leptospirosis, do you have any meningeal manifestations?

DR. DELLER: Yes, meningeal manifestations are seen; in fact, the patients frequently will have what is thought to be meningismus. The same manifestations will be seen in scrub typhus. We followed several patients clinically and found that the lymphadenopathy which developed in the cervical areas after several days is probably what was initially mistaken as meningismus. In a few cases we performed spinal taps, and the taps were negative. I think the tender cervical adenopathy often will be masquerading as meningismus.

QUESTION: Have you witnessed any outbreaks of plague?

DR. DELLER: So far as I know we have had only three cases of plague in American servicemen. As you know, plague immunizations have been quite effective. The current plague immunization program, apparently, is keeping the incidence of plague in the American soldier quite low. Certainly plague is very high in the Saigon area and throughout Southeast Asia. We see large numbers of cases in the population there. I am just hopeful that we will be able to continue with our luck in keeping this disease suppressed in the American population.

*Rudi Schmid, M.D., Professor of Medicine.

REFERENCES

1. Deller, J. J., and Russell, P. K.: An analysis of fevers of unknown origin in American soldiers in Vietnam, Ann. Intern. Med., 66:1129, 1967.

2. Ross, R. W.: The Newala epidemic. III. The virus: Isolation, pathogenic properties, and relationship to the epidemic, J. Hyg., 54: 177, 1956.

3. Deller, J. J., and Russell, P. K.: Chikungunya disease, Amer. J. Trop. Med. Hygiene, 17:107, 1968.

4. Skrzypek, G., and Barrett, O.: The problem of vivax malaria in Vietnam returnees. Part II. Malaria chemoprophylaxis survey, Military Medicine, 135:449, 1968.

5. Weber, D. R., Douglass, L. E., Brundage, W. G., and Stallkemp, T. C.: Acute varieties of melioidosis occurring in US soldiers in Vietnam, Amer. J. Med., 46:234, 1969.